REMARKS

This Reply is in response to the non-final office action issued on October 29, 2010. Claims 5-25, 28-30, 32-34,56-58, 62, 67-72, 75-76, and 79-83 are currently pending. Claims 9-25, 28-30, 32-34, 36, 56-58, 62, 67-72, 75,76, and 79-83 are withdrawn from consideration as drawn to non-elected subjection matter. Claim 5 has been amended to better define the invention. Thus, the claims presently under consideration are claims 5-8 as set forth herein. These claims are supported by the specification as filed, and Applicant believes that no new matter has been added. Applicant respectfully requests that the Examiner reconsider and withdraw the various grounds of rejection of the claims.

I. Rejection to the Specification.

The Examiner objects to the specification of the application as filed, for exceeding 150 words and for including legal phraseology. Applicant has amended the abstract herein thus rendering this objection moot.

II. Rejection under 35 U.S.C. 112, First Paragraph

Claims 5-8 have been rejected under 35 U.S.C. 112, first paragraph. The Examiner states that the specification does not reasonably provide enablement for a method of identifying or detecting any cancer. Applicant traverses this rejection and respectfully requests the Examiner reconsider the arguments provided in the September 28, 2010 response as well as those set forth below.

A "diagnostic assay" is known to mean an assay that can be used to help diagnose a condition. Final diagnosis is generally determined after evaluating the results of several screening assays. According to the MPEP, "to enable a diagnostic assay use, a disclosure **merely needs to teach how to make and use the assay for screening purposes**." MPEP III. (A)(2)(b)(ii)(b). Applicant has revised the preamble of the claim to read "A *diagnostic assay* for cancer or a pre-cancerous condition in a mammal". If the Examiner believes an alternative or further amendment would better define the claims as a diagnostic assay, Applicant requests such feedback.

Thus, contrary to the examiner's assertion, the present invention is **not** in the class of inventions characterized as the unpredictable arts. Indeed, based upon the MPEP this invention as claimed requires a lower level of descriptive enablement; that is, the specification: **merely needs to teach how to make and use the assay for screening purposes.** Applicant has provided 1/ the sequence to be measured (HSPC150 gene); 2/ the phenotype to be determined (copy number) and 3/ example means of determining copy number (including but not limited to fluorescent in situ hybridization)

The Examiner states that "the nature of the invention requires a reliable association between an increased copy number of the HSPC150 gene and the presence of cancer or a precancerous condition in a mammal". Applicant disagrees. A diagnostic assay merely assists in a diagnosis. All diagnostic assays are subject to some level of false results. A diagnosis is generally made after reviewing the results of one or more diagnostic assays in view of all relevant and available facts including but not limited to the patient's medical history. Applicant does not know what is meant by a "reliable" association. Is this to mean 100 percent? Is this to

mean 50 percent? As an example of the relationship applicant has shown that the subject gene (HSPC150) is related to breast cancer (see page 28, line 17 of the application as filed, also see Table 1, at gene No 119.) It is noted that at the end of the day, true utility of any given biotechnology innovation – at least so far as use in human - is determined by the FDA and related regulatory organizations, and eventually by the marketplace.

The examiner implies that the claims are over-broad stating: "the claims encompass a method wherein the cancer or precancerous condition is any type of cancer [...] in any type of mammal [...] wherein the cell or tissue is derived from anywhere". Applicant submits that this is not relevant. The claims are directed to the diagnostic test. The steps of the test are clearly recited. Any tissue can be tested. Any mammal can be tested. A user practicing the invention simply obtains a tissue sample from a mammal suspected of having cancer or a pre-cancerous condition and determines the gene copy number of the HSPC150 gene. The user then compares this value to a gene copy number of HSPC150 gene from tissue sample of a mammal of the same species that does not have cancer. There is no undue experimentation by the user. The user simply runs the test and makes a decision using this test in conjunction with other knowledge and/or other tests.

The Examiner states that Table 1 is problematic and requests clarification as to whether HSPC150 was over expressed, had an increased copy number, or both. Applicants have stated in prior responses and respectfully note here again, that Table 1 is a list of genes identified in cancerous cells as being *both* over-expressed and showing increased copy number. For support, please look to pages 7-10 of the specification as filed where the procedure for generating the list of genes found in Table 1 is summarized. For example, on page 8, the specification states:

"Combining genomic DNA analysis of gains and losses in the tumor cell lines/clinical samples with cDNA expression analysis from matched tumor types {...]" . Two steps are then elucidated. Step 1 relates to generating differential gene expression profiles and step 2 relates to generating a list of genes within the clustered regions of gains/losses for each cell type/tumor type to generate gene sets. Further support is found in the listed algorithm. For example, if one looks to the first two steps of the algorithm: the first step matches chromosomal regions of amplifications/gains with locations of genes/ESTs; then the second step further identifies genes/ESTs overexpressed in tumor tissue compared to normal. Additional support is found from the following two statements on Page 10:

- "the genes disclosed herein are expressed at levels in cancer cells that are different from the expression levels in non-cancer cells."; and
- "These genes as identified in Table 1 are amplified in cancer cells relative to non-cancer cells of corresponding tissues [...]"

Therefore the genes in Table 1 are genes that have been identified in cancerous cells as being BOTH over-expressed AND showing increased copy number. Given that HSPC150 is included on this list, the specification does therefore not only provide adequate support of the HSPC150 gene having an increased copy number in cancer or pre-cancerous conditions; it provides explicit support.

Applicant further directs the Examiner to the included Declarations.

The Examiner then points to the level of experimentation asserting that there is "no evidence in the specification that increased copy number of HSPC150 is actually associated with cancer or precancerous conditions, thereby necessitating undue experimentation [...].". First

Applicant notes that working examples are *not* required by the statute, rules or the case law. Second, the Applicant reminds the Examiner that the claims pending herein are directed to a diagnostic test. In the present situation the level of skill in the art is know to be high – and the level of enablement required for a diagnostic test low, (given that a diagnostic test is **not** in the class of inventions characterized as the unpredictable arts). The present specification provided considerable direction and guidance on how to practice the claimed invention, particularly given the high level of skill in the art at the time the application was filed.

Applicant respectfully submits that the current disclosure adequately describes the method of practicing the invention. Considering the scope of claims and the description of the current disclosure, together with the predictability of the state of art, and the general level of one of ordinary skill in the art, Applicant maintains that the specification meets the enablement requirements set forth under 35 U.S.C, 112, 1st paragraph.

III. Rejection under 35 U.S.C. 103

The Examiner has rejected claims under 35 USC 103 as being unpatentable over Crawley. Applicant respectfully traverses this rejection.

At the outset, Applicant notes that the Examiner is being inconsistent with arguments. Related to enablement above, the Examiner has argued that "it is highly unpredictable as to whether the results obtained with hepatocellular carcinoma could be extrapolated to other cancers and pre cancerous conditions." The Examiner then cites this *same* reference as a reference rendering the present invention obvious.

Applicant further notes that claim 7 is directed to specific cancers wherein the cancer is breast cancer, colon cancer, lung cancer, prostate cancer, ovarian cancer, pancreatic cancer, cervical cancer and kidney cancer. As stated above, Crawley is directed to hepatocellular carcinoma.

Crawley discloses use of comparative genomic microarray analysis to predict regions of cytogenic change by searching for regional gene-expression biases. Comparative genomic microarray analysis (CGMA) is an *indirect* means of identification from gene expression studies. In Crawley, CGMA was applied to hepatocellular carcinoma (HCC) gene expression profiles.

Applicant further notes the following:

- The conclusion of Crawley states: "CGMA *might* be useful for identifying *candidate* genes within cytogenetically abnormal regions." (Emphasis added.)
- Gene expression ratios were determined as follows: log-transformed non-cancerous tissue ratios (N/U) were subtracted from the log-transformed HCC tissue ratios (T/U) for each gene such that log2(T/N) = log2(T/U) - log2(N/U). If an HCC sample did not have a corresponding non-cancerous sample, the global mean of the non-cancerous tissue gene-expression ratios were used. Again, this is an *indirect* method.
- "To identify *regional gene-expression biases*, gene-expression values that map within a given chromosomal arm were collected and a sign test for a one-sample mean/median was used to determine whether a significant upward or downward bias was present in the expression values. An exception was made for chromosomes 13-

16, 21 and 22. These chromosomes are more telocentric and therefore only their q-arms were tested for expression biases." (Emphasis added.)

Crawley does not teach or suggest a diagnostic assay for cancer

Crawley therefore discloses an alternative to comparative genomic hybridization cytogenic profiling when gene-expression profiling data is available. Crawley does not provide *any* teaching related to the use of *any* of the genes listed in the reference in a diagnostic assay for cancer.

Crawley does not teach or suggest determining copy number of HSPC150 gene in suspect tissue and comparing to copy number of HSPC150 gene in normal tissue

The term "copy number" cannot be found in the Crawley reference. The reference neither teaches nor suggests obtaining a copy number for *any* of the genes listed within the reference. Rather, this reference discusses determining an overall upward or downward bias in expression values from multiple genes and using the combined total to identify a trend.

Crawley does not teach or suggest that HSPC150 amplification is indicative of cancer

Crawley does not *predict* that the HSPC150 gene is amplified in HCC samples as stated by the Examiner. This gene is simply identified along with over 30 others in the experimental results section of the paper as being a gene "whose expression changed at least twofold in 70% of the tumor samples in the same relative direction as the cytogenic change and are located in regions identified as cytogenetically abnormal by CGMA in at least 35% of samples".

In contradistinction to Crawley, the present inventors have provided a diagnostic assay for cancer or a pre-cancerous condition by determining the HSPC150 gene copy number for a suspect sample and comparing it to the HSPC150 gene copy number for a normal sample.

The determination of obviousness is not whether a person could, with full knowledge of the patented device, reproduce it from prior art or known principles. The question is whether it would have been obvious, without knowledge of the patentee's achievement, to produce the same thing that the patentee produced. This judgment must be made without the benefit of hindsight.

The elegant simplicity of the diagnostic test disclosed by Applicant is not inimical to patentability. The patent statute does not require an invention to be complex to be patentable. Indeed, the present invention provides a solution to a critical need. Conventional chromosome banding techniques known at the time of the invention allowed for the detection of specific chromosomal defects in tumor cells. However interpretation of the banding pattern was difficult. This was particularly the case when complex chromosomal rearrangements or subtle abnormalities were present. Applicant provides to the public a means of using techniques such as based upon fluorescent *in situ* hybridization in a diagnostic assay for cancer or pre-cancerous condition.

Applicant therefore submits that Cawley neither discloses nor suggests the invention as defined by claim 5, upon which claims 6 and 8 depend. Applicant further submits that upon a review of Cawley, at the time the invention was made, the present invention as defined by claims 5, 6, and 8 would not have been obvious to one of ordinary skill in the art.

IV. Conclusion

In view of the foregoing remarks, Applicant respectfully requests the timely allowance of the pending claims. Should the Examiner believe that any further action is necessary to place this application in better form for allowance, the Examiner is invited to contact Applicant's representative at either the telephone number listed below or Applicant's cell phone 443-831-2937.

Applicant hereby petitions for an Extension of Time to reply within the third (3rd) month following the shortened statutory period to respond. The commissioner is authorized to charge any required fees ("small entity" status) to Deposit Account No. 50-4364.

Respectfully Submitted,

/Gianna Julian Arnold /

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